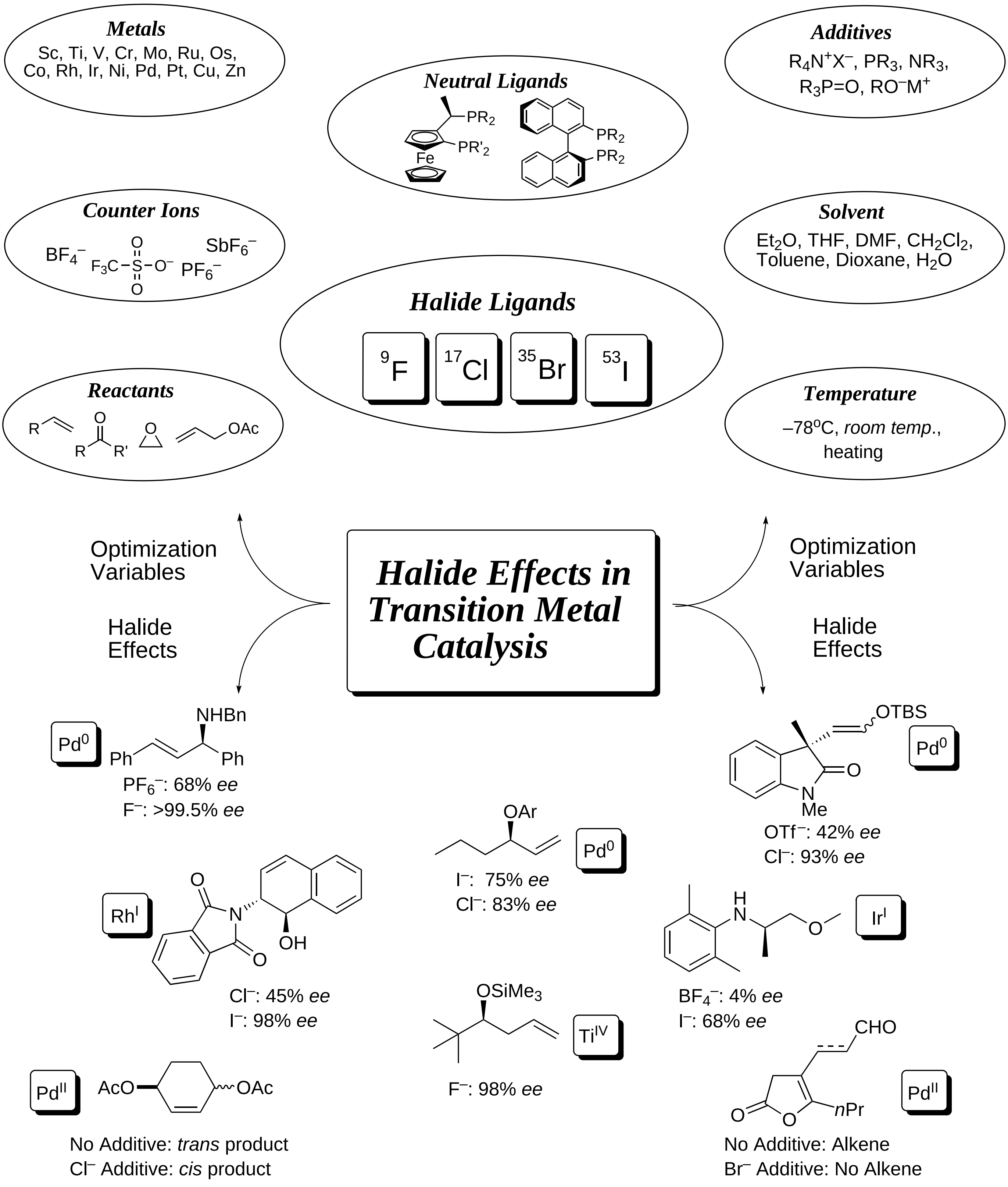

Halide Effects in Transition Metal Catalysis

Metals
Sc, Ti, V, Cr, Mo, Ru, Os,
Co, Rh, Ir, Ni, Pd, Pt, Cu, Zn

Neutral Ligands

Additives
$R_4N^+X^-$, PR_3, NR_3,
$R_3P{=}O$, RO^-M^+

Counter Ions
BF_4^- $F_3C{-}SO_2{-}O^-$ SbF_6^- PF_6^-

Solvent
Et_2O, THF, DMF, CH_2Cl_2,
Toluene, Dioxane, H_2O

Halide Ligands
^{9}F ^{17}Cl ^{35}Br ^{53}I

Reactants

Temperature
–78°C, *room temp*.,
heating

Optimization Variables

Halide Effects

Pd^0
PF_6^-: 68% *ee*
F^-: >99.5% *ee*

Pd^0
OTf^-: 42% *ee*
Cl^-: 93% *ee*

Pd^0
I^-: 75% *ee*
Cl^-: 83% *ee*

Rh^I
Cl^-: 45% *ee*
I^-: 98% *ee*

Ir^I
BF_4^-: 4% *ee*
I^-: 68% *ee*

Ti^{IV}
F^-: 98% *ee*

Pd^{II}
No Additive: *trans* product
Cl^- Additive: *cis* product

Pd^{II}
No Additive: Alkene
Br^- Additive: No Alkene

Halide effects have been discovered in many transition metal catalyzed processes and have become an important aspect of catalyst optimization.

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Halide Effects in Transition Metal Catalysis

Keith Fagnou and Mark Lautens*

Dedicated to Professors B.M. Trost and D.A. Evans on the occasion of their 60th birthdays

Among the most common ligands found on transition metal catalysts are halide ions. Of the commercially available catalysts or pre-catalysts, most are halo–metal complexes. In recent years, manipulation of this metal-halide functionality has revealed that this can be used as a highly valuable method of tuning the reactivity of the complex. Variation of the halide ligand will usually not alter the nature of the system to the extent that it becomes unreactive but will impart sufficiently large changes that differences in reactivity or selectivity occur. These differences are a product of the steric and electronic properties of the halide ligand which has the ability to donate electron density to the metal occurs in a predictable manner. Despite the common perception in asymmetric catalysis that halide ligands are of secondary importance compared to chiral ligands, halide ligands have been found to exert dramatic effects on the enantioselectivity of asymmetric transformations. While the mechanism of action is known for relatively few of the cases, many intriguing and potentially synthetically useful trends are apparent. This review discusses the physical properties of the halides and their effects on stoichiometric and catalytic transition metal processes. The metal-halide moiety thus emerges as a tunable functionality on the transition metal catalyst that can be used in the development of new catalytic systems.

Keywords: asymmetric synthesis · halogens · homogeneous catalysis · ligand effects · transition metals

1. Introduction

The important role of spectator or ancillary ligands in transition metal ligand-substitution reactions has long been recognized. Through judicious choice of the ancillary ligands, it is often possible to alter the steric and electronic properties of the metal and therefore influence the course of many transition metal processes. Within the field of transition metal catalysis, catalysts containing halide ligands are ubiquitous, a result of the stability of the metal–halide bond. Despite the prevalence of this functionality, a full appreciation of its utility in catalyst development has only recently become widespread. As ancillary ligands, halides can provide an invaluable handle with which the reactivity and selectivity of a catalyst can be fine-tuned for a given transformation.

In asymmetric catalysis, attention is primarily paid to the choice of metal and chiral ligand, this is because of the inherent difficulty in selecting a chiral ligand that will give high enantioselectivities. For this reason, halide ligands within the coordination sphere are often regarded as being of limited importance. In fact, most discussions of halide ligands involve their removal from the coordination sphere and replacement with weakly coordinating anions such as triflate, hexafluorophosphate, and hexafluoroantimonate.[1] Investigations into the role of halide spectator ligands are far less frequent. When these reports are brought together, intriguing trends appear which could prove useful in the development of new catalytic asymmetric transformations.

The body of this review has been divided into three sections. In the first section, emphasis is placed on understanding how the physical properties of the halides will influence the behavior of the metal complex as a whole. The second section deals with stoichiometric transformations involving transition metal halide complexes where the halide has been found to influence the reactivity of the system. By learning how halide ligands can influence stoichiometric transformations, a better understanding of halide effects in catalytic transformations can be gained. Catalytic processes that involve halide effects are presented in the third section. Emphasis in this section is placed on the experimental evidence for halide effects and selected asymmetric catalytic transformations are presented

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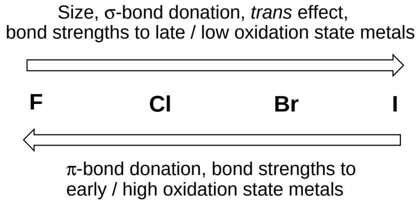
first. Understanding the influence of ancillary ligands on the enantioselectivity can be a challenging issue since it is often very difficult to pinpoint the precise enantiodiscriminating step in many catalytic processes. Despite this limitation, several reactions have appeared where the halide has been found to dramatically affect the enantioselectivity of the transformation. Halide effects have also been observed in achiral catalytic transformations. Since the mechanisms of several achiral processes are known, it is often possible to deduce how the halide ligand is influencing the transformation.

The chemistry of salt effects in organic and organometallic chemistry has been previously described in an excellent review which can serve as a starting point for the material covered herein.[2] This review will focus predominantly on the work that has appeared since 1992 that deals with the effect of changing the nature of the halide ligand on a transition metal complex. The effect of changing the nature of the "non-coordinating" ligands of cationic complexes will not be addressed.[3]

2. Understanding Halide Effects

2.1. Properties of Halide Ligands

The most important properties of the halide ligands include: 1) steric properties, 2) electronic properties (σ and π bonding), 3) polarizability, 4) nucleophilicity, and 5) the *trans* effect. The trends of these properties are outlined in Scheme 1.



Scheme 1. Trends in the properties of halide ligands.

2.2. Steric Properties of the Halides

The relative size of the halide ligand can play a decisive role in reactions where the halide is *cis* to the reaction site or on metal complexes with high coordination numbers. For example, as the steric bulk of a ligand increases, oxidative addition processes can be slowed while reductive elimination may be favored as a means of reducing the steric interactions. The steric bulk of halide ligands increases down the group in terms of ionic radii, covalent radii,[4] and cone angle[5] (Table 1).

Table 1. Steric properties of the halides.

	F	Cl	Br	I
Ionic Radius [Å]	1.36	1.81	1.95	2.16
Covalent Radius [Å]	0.709	0.994	1.142	1.333
Cone Angle [°]	92	102	105	107

2.3. Electronic Properties: σ and π Bonding

Predicting the nature of the interactions between a halide ligand and a transition metal is a complicated issue because

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M. Lautens


K. Fagnou

Keith Fagnou was born in Saskatoon, Saskatchewan Canada in 1971. He received his bachelors degree in education with distinction (B.Ed.) from the University of Saskatchewan in 1995, and after teaching for one year continued his studies at the University of Toronto. In 1998, he joined the research group of Prof. Mark Lautens working in the area of transition metal catalysis. In 2000 he received his M.Sc. and is currently conducting Ph.D. studies in the same area.

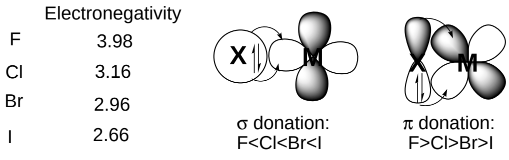
these interactions rely not only on the nature of the halide ligand, but also on several properties of the transition metal complex, including:

1. the transition metal and its oxidation state (number of d electrons)
2. the coordination number and geometry
3. the nature of the other ligands within the coordination sphere.

These factors are interrelated since a change in one can affect the others. They must therefore be regarded globally when considering the nature of the interactions of a halide ligand.

2.3.1. The Nature of the Halide Ligand

It is generally appreciated that the electronegativities of the halogens increase up the group, with fluorine being the most electronegative element. As a consequence of the halide electronegativities and the availability of their s electrons, the ability to form σ bonds increases down the group (Scheme 2). In the absence of other interactions between the halide and the metal, iodide would be expected to form the strongest bonds and donate the most electron density to the metal by these σ interactions. This is rarely the case, however, since π interactions commonly occur between the halide lone-pair electrons and the metal d orbitals.[6] When π interactions predominate, the opposite trend in electron donation to that predicted by electronegativity can be observed, and fluorine is the strongest π donor.[7]

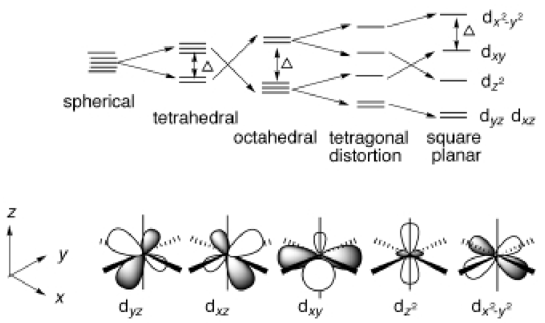


Scheme 2. Electronic properties of halide ligands.

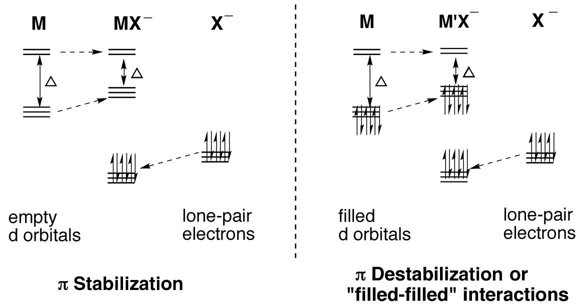
2.3.2. Effect of the Transition Metal Complex on π Bonding

For π interactions to be possible with transition metals, a metal orbital of appropriate symmetry must be available to interact with the halide lone pairs. The d orbital degeneracies and relative energies will be affected by the coordination geometry of the complex and can be predicted by the ligand-field model (Scheme 3).

The ways π bonding will influence the reactivity of a complex can be revealed by determining whether the π donation will have a stabilizing or destabilizing effect. The number of d electrons on the metal center must be considered and if there is an empty d orbital of suitable geometry a net stabilization can result. If the d orbital is fully occupied, a net destabilization termed "filled–filled" interactions will occur (Scheme 4).[6] As the d electron count increases from d^0 to $\mathrm{d}^6_{\mathrm{LS}}$, (LS = low spin) the effects of π donation will become more destabilizing in nature.



Scheme 3. Ligand-field splitting for common coordination geometries.



Scheme 4. π Stabilization and destabilization arising from molecular-orbital interactions for an octahedral coordination geometry.

While it may be anticipated that square-planar 16-electron d^8 complexes would possess significant π bonding to stabilize the low electron count, this is not the case; the only empty d orbital, $\mathrm{d}_{x^2-y^2}$, does not possess the appropriate symmetry to allow overlap with the halide ligand lone-pair electrons. The only orbitals with appropriate geometry, d_{yz}, d_{xz}, and d_{xy}, are filled and any interactions between these orbitals and the halide lone-pair orbitals will be destabilizing in nature.

When a π-acid ligand is coordinated to a square-planar 16-electron d^8 complex, however, some π donation will be observed. This is because the presence of strong π acids, such as carbonyl and nitrosyl ligands, can act to reduce the influence of filled–filled interactions through a "push–pull" mechanism. The CO ligand, for example, can accept electron density into its π*-antibonding orbital which will reduce the electron density of the occupied metal d orbitals ("pull") and therefore reduce the degree of filled–filled destabilization produced through halide ligand π donation ("push"). In d^8 square-planar complexes this push–pull mechanism results in a reduction of electron density in the occupied d_{yz}, d_{xz}, and, d_{xy} orbitals and permits π donation when π-acid ligands are present. This explains, for example, why π donation from the halide ligands (X) is observed in Vaska-type complexes, $[\mathrm{Ir(PR_3)(CO)X}]$.

Consideration of the coordination geometry and the presence of π effects is relevant if an intermediate along the reaction pathway contains 14- or 16-electrons.[6] The donating ability of the halide ligand can stabilize coordinative unsaturation and low electron counts making this step in the process more favorable. The reverse is also true. For example, the addition of a sixth ligand to a 16-electron d^6 complex to give an 18-electron octahedral product will be disfavored by the presence of strongly π-donating ligands, a result of unfavorable filled–filled interactions. These concepts are illustrated in Section 3.2.

2.4. Hard/Soft Interactions and Polarizability

As a general rule of thumb, it can be said that a *hard* species will prefer to bind other *hard* species and *soft* will bind *soft*. With regard to the halides, their relative polarizability or softness is expected to increase down the group.[8] The hard/soft character of the transition metals follows expected trends. A transition metal will become softer in character as its oxidation state is lowered, the further down the group it lies, and the further to the right in the transition metal series it is found. It can be expected that as a transition metal becomes softer in character it will increasingly prefer to bind the heavier halides. On the other hand, high-oxidation state hard metal centers will prefer to bind to ligands which can better donate electron density to the metal and so would prefer to bind fluoride. Experimental evidence supports these predictions.[9–11]

Evidence for the importance in considering these hard/soft interactions can be found in the relative formation constants for various $M{-}X^{n+}$ species. From Table 2 it can be seen that H^+ and Zn^{II} are hard in nature and will preferentially bind to fluoride. The Cu^{II} center is a borderline case showing little variation among the halides, while the Hg^{II} ion should be considered as soft since it binds strongest to iodide.[12] Further experimental evidence for these types of interactions lies in the relative rates of aquation for complexes of type $[M(NH_3)_5X]^{2+}$ where $M = Co^{III}$, Cr^{III}, Ru^{III}, Rh^{III}, and Ir^{III} (Table 3).[13] For the harder metals, Co^{III} and Cr^{III}, iodide is most easily displaced. The order is reversed for Rh^{III} and Ir^{III} where it is easier to displace the lighter halides. The Ru^{III} center is an intermediary case where there is no distinct trend. Thus, as one descends the group or moves right along a transition series, the soft character of the metal increases for a particular oxidation state.

Table 2. Formation constants for hard and soft acids and bases.

	F^-	Cl^-	Br^-	I^-
H^+	3	−7	−9	−9.5
Zn^{2+}	0.7	−0.2	−0.6	−1.3
Cu^{2+}	1.2	0.05	−0.03	–
Hg^{2+}	1.03	6.74	8.94	12.87

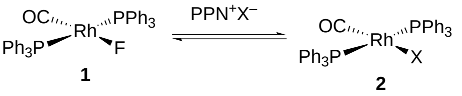
[a] Values are logarithms of equilibrium constant for $[M_{(aq)}]^{n+} + X^- \rightleftharpoons [MX_{(aq)}]^{(n-1)+}$.

The other ligands within the coordination sphere can also affect the hard/soft character of the metal. For example, with the $[Co(CN)_5X]^{3-}$ ion, fluoride is the most easily displaced halide indicating that the metal is behaving as a soft base, in contrast to the situation found for the $[Co(NH_3)_5X]^{2+}$ ion indicated above.[11] This example indicates that the CN ligands are able to impart a softer character to the Co center than are the hard NH_3 ligands.

Table 3. Rates of aquation k_{aq} [10^7 s^{-1}] of complexes $[M(NH_3)_5X]^{2+}$ with displacement of X^- at 25 °C.

	Co^{III}	Cr^{III}	Ru^{III}	Rh^{III}	Ir^{III}
I	83	10000	2.5	0.062	0.0019
Br	39	950	9.8	0.34	0.011
Cl	18	95	7.1	0.48	0.011
F	0.86	2.5	–	–	–

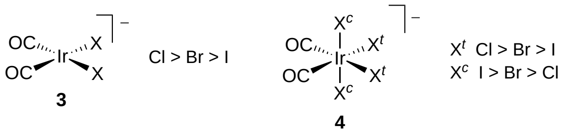
Further evidence for other ligands within the coordination sphere affecting the hard/soft character of the metal has been documented for metal–carbonyl compounds. For example, Forster and Hoffman showed that fluoride binds strongest to $[Rh(CO)(PPh_3)_2]^+$ ions under aprotic conditions.[14] An illustrative set of experiments involves the treatment of the rhodium–fluoride complex **1** with an equivalent of bis(triphenylphosphane)nitrogen halide (PPNX) and determining the equilibrium ratio of rhodium halides **1** and **2** (Scheme 5). From the these results it is evident that fluoride binds the strongest and iodide the weakest—opposite to what would be expected based on hard/soft arguments. This result can be rationalized by appreciating that push–pull interactions will occur between the halide and the *trans* CO ligand. Since these interactions will be maximal with the lighter halides, F will be most tightly bound.



X	**1/2**
Cl	63/37(±6)
Br	90/10(±1)
I	98/2(±1)

Scheme 5. Effect of push–pull interactions on the hard/soft character of a transition metal complex.

Another example of ligands affecting the hard/soft character of the metal is found with halocarbonyliridate complexes **3** and **4** (Scheme 6).[14a] The influence of the *trans* CO ligands is again observed with **3** to which Cl is preferentially bound.



Scheme 6. Differential effect of push–pull interactions at *cis* and *trans* coordination sites.

Complex **4** is particularly illustrative, since the presence of the *cis* CO ligands results in halide coordination sites that differ dramatically in their hard/soft character. As with **1**–**3**, the CO ligands on **4** result in a "hardening" of the corresponding *trans* coordination sites X^t. Since the push–pull effect is highly directional, the positions *cis* to the CO ligands X^c retain their soft character. Thus, at positions X^t, *trans* to the CO ligands where the push–pull effect is greatest, chloride is preferentially bound. At positions X^c, where there the electronic effect of the CO ligands is reduced, iodide is preferentially bound.

2.5. Nucleophilicity Parameters and the *trans* Effect

To quantitatively compare the relative nucleophilic abilities of various ligands, a nucleophilicity scale[15] has been established based on Pt^{II} centers.[16] In accord with the *soft* nature of the Pt^{II} center, iodide possesses the largest nucleophilicity parameter. Other quantitative results have only been obtained for Au^{III} centers[17] (which parallel the relative values observed for Pt), and this trend can be expected to be similar for other square-planar complexes containing soft transition metals.

The *trans* effect[18] is another important property of ligands that shows a distinct trend within the halide group. The *trans* effect is defined as "the effect of a coordinated group on the rate of substitution reaction of ligands *trans* to itself."[19] The relative *trans* effect of the halides has been determined quantitatively for Pt^{II} centers, with iodide possessing the largest *trans* effect. This trend for the halide group is related to their σ-donating ability since ligands which are strongly σ donating will strengthen their bond to the metal at the expense of the ligands *trans* to them. Indeed, calculations of the overlap between the σ-donor orbital of the halide ligands and the Pt 6p$_\sigma$ orbitals showed that there was increasing overlap on going from Cl to I.[20]

3. Halide Ligands and Stoichiometric Processes

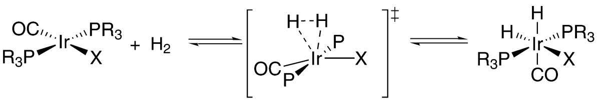
3.1. Electron Donation and Ease of Metal Oxidation

An increase in electron density at the metal center will facilitate oxidative processes.[21] When the effects of halide ligands on oxidative processes are considered, it is the ability to participate in π donation that predominates. For example, electrochemical studies on [Cp_2MX_2] (M = Nb, Ta; Cp = C_5H_5)[22] and [$Cp_2WX(R)$][23] revealed that the ease of oxidation increased I < Br < Cl. In another study,[24] it was found that reversible oxidation of [Cp*Fe(dppe)X] (dppe = bis(diphenylphosphino)ethane; Cp* = C_5Me_5) to the mono- and dicationic species occurs most readily for the most electronegative but best π-donating halide, F, and becomes more difficult down the series. It was also determined that as a result of the one- and two-electron oxidations, the Fe–X bonds were weakened with the Fe–F bond weakening the least—again indicating the pronounced effect of halide-to-metal π donation which becomes more significant with the removal of electrons.

3.2. Hydrogen Addition/Elimination

The effects of the halide ligands on the reactivity of *trans*-[$Ir(PR_3)_2(CO)X$], [$IrXH_2(PR_3)_2$], and *trans*-[$M(PMe_3)_4X_2$] (M = Mo, W) towards hydrogen addition illustrate very well the concepts described in previous sections. To explain the observed trends, halide–metal π donation as well as push–pull and filled–filled interactions must be considered. Furthermore, they underline the point that by changing the halide ligand, dramatic effects on the reactivity can be obtained. They also demonstrate that these influences may not be the same for a given reaction when performed with different transition metal systems.

The dependence of the rate of oxidative addition of hydrogen to *trans*-[$Ir(PR_3)_2(CO)X$] (Vaska-type complexes) on the halide ligand has been studied in detail. Both experimental[25] and computational[26] studies reveal that the addition of H_2 is most exothermic when X = I.[27] While oxidative addition should be favored by ligands which increase the electron density at the metal,[28] the trend here appears to contradict this expectation since F, the strongest π donor, produces the least energetically favorable reaction. To verify that the relative π-donating abilities of the halides followed the anticipated trend, the ν(CO) stretching frequencies were examined for **5**. These frequencies indicate that the electron density at the metal does indeed increase according to the predicted ability of the halides to donate electron density by π donation (I < Br < Cl < F) exactly *opposite* to the observed trend in reactivity (Scheme 7).[29, 30] This discrepancy is best explained by appreciating how changes in the coordination geometry affect the role of the π donation.



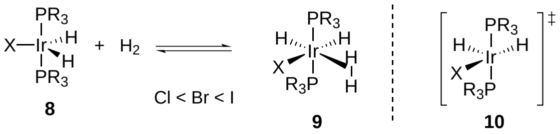
5 (16 e⁻) **6** **7** (18 e⁻)

	ΔH_{exp}[kcal mol^{-1}]	$\tilde{\upsilon}$(CO) [cm^{-1}] (**5**)
F	>-10	1957
Cl	-14	1965
Br	-17	1966
I	-19	1967

Scheme 7. Halide effects in hydrogen addition to Vaska's complex.

Goldman and Krogh-Jespersen have demonstrated that Ir–X π interactions dominate the thermodynamics of H_2 addition in at least three ways. First, π donation, made possible on the square-planar complex through the presence of the π-acid CO ligand, can stabilize the 16-electron d^8 square-planar complex **5**. Thus **5** will be most stable when X = F. Second, π donation will destabilize the 18-electron d^6 H_2-addition product **7** through filled–filled interactions. Complex **7** will therefore be least stable when X = F. Third, π donation was also found to influence the energy of the transition state **6**. In the starting material **5**, π bonding occurs as a result of the push–pull interactions between the *trans* halide and carbonyl ligands. This effect is highly directional and will be maximal when the ligands are *trans* to each other. To reach the transition state, a bending of the X-Ir-CO unit is required. This bending will diminish the stabilizing push–pull interactions and will become more disfavored as π donation increases, reaching a maximum when X = F. An argument is also made that the reactivity would be reduced as a result of an increase in the HOMO–LUMO gap because of π donation.[31] Since fluoride is the best π donor, the combination of these π effects will make H_2 addition to the fluoro-complex the least favorable of the halide series.

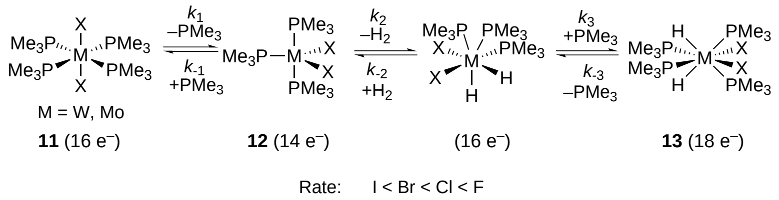
In a second example, the rate of H_2 addition to [$IrXH_2(PR_3)_2$] (**8**) was found to vary with X, the rate being most favorable when X = I (Scheme 8).[32] This reaction has been studied computationally.[33] To accommodate H_2 binding, distortion of the Ir trigonal-bipyramidal complex **8** towards the T_H-shaped (a square pyramid with an H atom at the apex) transition state **10** was proposed.[34] While halide to metal π donation can occur in **8**, this interaction is either



Scheme 8. Halide effects in hydrogen addition to $[IrXH_2(PR_3)_2]$ and the T_H transition state **10**.

partially or completely disrupted in the T-shaped transition state.[35] It is therefore more energetically difficult to reach the transition state as the level of π donation increases, and will be most difficult for Cl and F ligands. Furthermore, the distortion to the T-shaped transition state places the hydride and the halide *trans* to one another. Since the hydride is a strong σ donor, placing iodide *trans* to it will be more favorable than chloride, because iodide is more polarizable and can therefore better adapt to the bonding requirement of the *trans* hydride. The stability of the product complex **9** will also be affected by the nature of the halide ligand. Since it is an 18-electron d^6 six-coordinate complex, any π donation from the halide ligand will result in filled–filled destabilizing interactions. The strongest π donors, Cl and F, will most disfavor the formation of **9**.

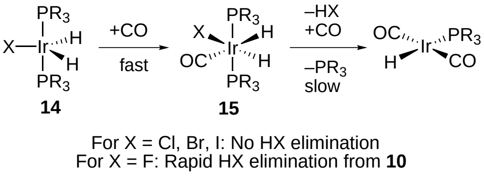
Friesner, Parkin, and co-workers have recently reported that the energetics of H_2 addition to **11** depend strongly on the halide, the addition being most exothermic for X = F (Scheme 9).[36] This trend is opposite to that found for Vaska's complex where the fluoride complex produces the least favorable reaction. To explain this difference, both the steric and the electronic properties of the halide ligands must be considered. Since fluoride is the smallest of the halides its presence would minimize the steric interactions on the highly congested eight-coordinate product complex **13**. From an electronic point of view, fluoride ligands will destabilize the starting material complex **11** through filled–filled interactions and make it more reactive towards phosphane dissociation. This destabilization would be less pronounced with the heavier halides. Fluoride would also best stabilize the unstable 14-electron intermediate **12** by π donation.



Scheme 9. Halide effects in hydrogen addition to *trans*-$[M(PMe_3)_4X_2]$ (M = Mo, W).

3.3. HX Elimination

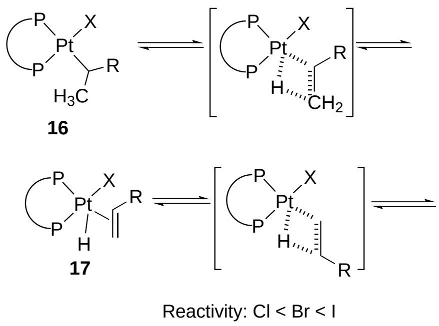
Caulton has studied the effect of halide ligands on the rate of HX elimination from $[Ir(H)_2X(PtBu_2Ph)_2]$ (**14**) which is promoted by CO coordination (Scheme 10).[37] Experimental results confirmed the prediction that upon coordination of the CO ligand, the destabilization created by filled–filled interactions involving the orbitals of the X ligand at the 18-electron d^6 six-coordinate metal center affect the rate of HX elimination. With the weaker π donors (Cl, Br, I), no HX elimination was observed from **15**. With fluoride, on the other hand, rapid HX elimination was observed after a few minutes at room temperature, which correlates well with the strong π-donating ability of fluoride relative to the heavier halides.



Scheme 10. Halide effects in HX elimination.

3.4. *β* Hydride Elimination

Recent studies of *β* hydride migrations in $[PtL_2(X)CHRCH_3]$ (**16**) have revealed a dependence of rate on the nature of the halide (Scheme 11).[38] The mechanism of these transformations shows that the intermediate five-coordinate complex **17** (of undefined geometry) is present in both forward and reverse processes. The rate dependence was proposed to be a function of the stability of this complex. It was shown for other five-coordinate palladium complexes that their stability increases in the order Cl < Br < I.[39] Thus, if the stability of intermediate **17** is affected analogously, the rate would be influenced correspondingly, being fastest for X = I.



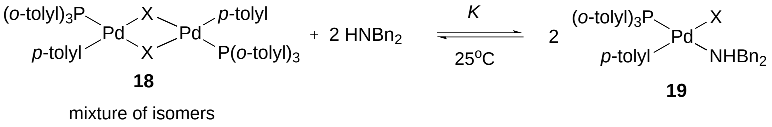
Scheme 11. Halide effect on the rate of *β*-hydride elimination.

3.5. Formation and Cleavage of Metal–Halide Dimers

In many catalytic processes, dimeric catalyst precursors are used or such species are implicated along the reaction pathway. While dimeric complexes are rarely the active species, their relative stability can influence the rate of the transformation by acting as a reservoir or resting position during the catalytic cycle. Experimental evidence has shown that the stability of these dimers changes dramatically with the nature of the halide, being most stable when bridged by iodide ligands.

While studying aryl amination reactions, Buchwald found that the nature of the halide affects the cleavage of the complexes **18**.[40] When dimeric palladium complexes **18** were treated with dibenzylamine, monomer formation was found to be most favorable for X = Cl (Scheme 12). It was also found that reaction with smaller amines, such as dibenzylamine, favored cleavage more than larger ones, such as diisopropylamine. Furthermore, this difference in reactivity was more enhanced when X = I than when X = Cl.

Buchwald explained these trends based on the relative polarizability and size of the halides. The dative Pd-(μ-X) bond strengths should parallel the donor ability of the halide lone-pair electrons and therefore be strongest when X = I.



X	K[M^{-1}]	G[kcal mol^{-1}]
Cl	(6 ± 1) x 10^3	–5.6
Br	(3.5 ± 0.5) x 10^3	–5.1
I	90 ± 20	–2.9

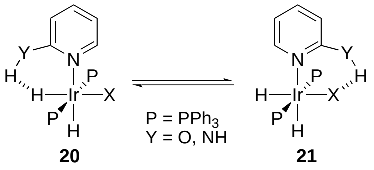
Scheme 12. Effect of halide on the cleavage of dimers.

The dependence of the rate of dimer cleavage on the size of the amine and the halide ligand can be explained as follows: since the amine and the halide ligands are *cis* in the monomeric species **19**, a larger halide will create a weaker Pd–N bond and disfavor cleavage. Furthermore, large amines should promote Pd–N bond weakening since steric interactions with the halide would be more severe.

The stability of iodide-bridged dimers has been documented elsewhere.[41,42] For example, when PdI_2 is treated with excess P(o-tolyl)$_3$, only the dimeric species is obtained. On the other hand, when $PdBr_2$ or $PdCl_2$ are used, only the monomers, [Pd{P(o-tolyl)$_3$}$_2$X$_2$], are formed.[41] Chatt and coworkers also observed that treatment of dimeric [{Pd(P*n*Pr$_3$)$_2$Cl}$_2$] with *p*-toluidine formed the stable amine monomer [Pd(P*n*Pr$_3$)$_2$(*p*-toluidine)Cl] while reaction of the iodide-bridged dimer produces an equilibrium mixture of starting material and the monomeric species [Pd(P*n*Pr$_3$)$_2$(*p*-toluidine)I].[42]

3.6. Hydrogen Bonding and Protonation

Hydrogen bonding has been shown to occur between weak acids, such as OH and NH, and transition metal complexes, either at the metal center itself or at its ligands.[43] A quantitative study, by Eisenstein and Crabtree, designed to examine competitive hydrogen bonding to halide and hydride ligands is illustrative.[44] By determining the relative population of the two isomers **20** and **21**, the relative ability of the halide ligand to participate in hydrogen bonding could be deduced. A distinct trend was found within the halide series, with fluoride being most able to participate in H bonding (Scheme 13). Additional experimental evidence for considering these halide hydrogen-bonding interactions is revealed by the increasing number of crystal structures of transition metal complexes which contain these bonds.[45]

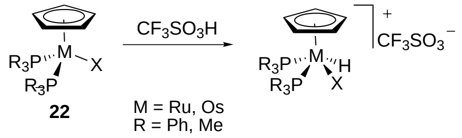


X	IrX-HN	IrH-HN
I	<1.3	3.3
Br	1.8	3.0
Cl	2.1	2.9
F	5.2	<2.9

Scheme 13. Relative ability of the halides to H bond. The Table shows the calculated bond strengths of the H bonds [kcal mol^{-1}].

Eisenstein and Crabtree also found that the halide ligand on **20** and **21** influenced the ability of the hydride ligand *trans* to the halide to hydrogen bond, with the iodo complex producing the strongest iridium–hydride–H bonds. This result was rationalized in terms of the relative *trans* influence of the halides. A larger *trans* influence would lengthen the *trans* Ir–H bond and displace electron density towards the hydride ligand. This increase in electron density would result in an increase in the ability of the hydride ligand to hydrogen bond. Iodide, which possesses the largest *trans* influence of the halides, is thus the most able to increase the H-bond strength at the *trans* hydride ligand.

Angelici has reported the enthalpies of protonation for a wide variety of transition metal complexes, and these too were found to be influenced by the halide ligand.[46] For ruthenium and osmium complexes of type **22**, the basicity was found to be highest when X = F (Scheme 14) and this was rationalized in terms of electronic and steric effects. From an electronic point of view, fluoride is the strongest π donor and should therefore most increase the electron density at the metal center. From a steric point of view, fluoride would result is the least steric congestion as the complex coordination number increases and less space is available within the coordination sphere.



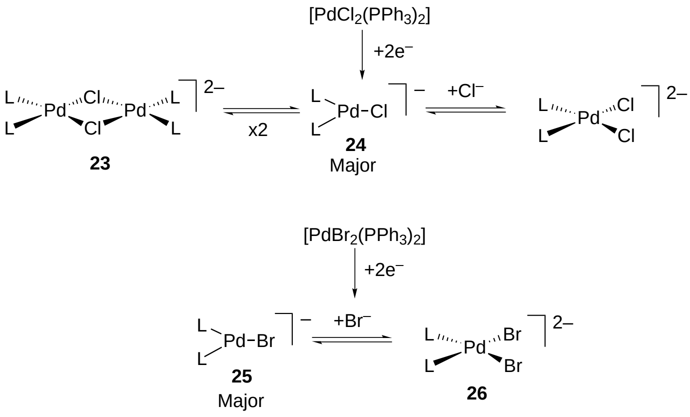
X	M = Ru R = Me	M = Os R = Me	M = Os R = Ph
	$-\Delta H_{HM}$ [kcal mol^{-1}]		
I	20.6	26.6	14.1
Br	20.9	29.4	16.3
Cl	21.2	–	19.7
F	–	–	37.3

Scheme 14. Influence of halide ligand on the enthalpy of protonation.

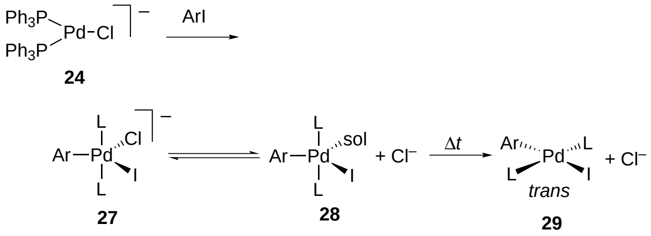
3.7. Generation of Anionic Palladium(0) and Oxidative Insertion

Palladium(0) is ubiquitous in transition metal catalysis. A number of methods are used to access this species, these include the use of [Pd(PPh$_3$)$_4$] and [Pd$_2$(dba)$_3$] (dba = dibenzylacetone), or reduction of [Pd(OAc)$_2$] and [PdL$_2$Cl$_2$] complexes. It has been demonstrated that when [Pd(PPh$_3$)$_4$] is used (under certain conditions), the coordinatively unsaturated 14-electron [Pd(PPh$_3$)$_2$] species is the active catalyst, even though it is present in very small amounts as a result of the unfavorable endergonic processes required for its generation.[47] Amatore and Jutand have recently shown that when in situ reduction of the Pd^{II} complexes is used to generate Pd^0, anionic species are generated instead of the neutral [Pd(PPh$_3$)$_2$] complex.[49] Futhermore, the nature of the halide was found to influence the reactivity of these palladate intermediates.

When the complexes [PdX$_2$(PPh$_3$)$_2$] (X = Cl, Br)[48] are reduced electrochemically, mixtures of anionic complexes are formed, the nature of which depends on the halide found on the precursor.[49] The effect of halide binding was found to have a stabilizing effect on the [Pd(PPh$_3$)$_2$] moiety since the reduced species did undergo rapid reaction to form metallic palladium. For example, when [PdCl$_2$(PPh$_3$)$_2$] is reduced, an equilibrium mixture of two monomeric and one dimeric species is formed were the predominant species is [Pd(PPh$_3$)$_2$Cl]$^-$ (**24**). With [PdBr$_2$(PPh$_3$)$_2$], only the monomeric species **25** and **26** are produced (Scheme 15).[49d]



Scheme 15. Anionic palladium(0) species generated through reduction of [PdX$_2$L$_2$] species.

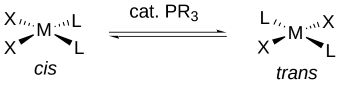


Scheme 16. Oxidative addition of PhI to [Pd(PPh$_3$)$_2$Cl]$^-$. Δ*t* tends to be in the region of several hours.

The reactivity of these equilibrium mixtures was investigated with respect to oxidative addition to phenyl iodide.[49c] Commencing with anionic Pd^0 complex **24** prepared in situ, oxidative addition of PhI generates a five-coordinate 18-electron anionic complex **27** where both the chloride and the iodide ligands remain bound (Scheme 16). Intermediate **27** is then involved in an equilibrium that generates neutral species **28** where the chloride ion has dissociated and is replaced by a solvent molecule. Subsequently, the *trans* square-planar complex **29** is produced. It was found that the addition of chloride ions inhibits the generation of **29**. Of the three chloride species generated by the reduction of [PdCl$_2$(PPh$_3$)$_2$], the dimer **23** is the most reactive, but because of its low concentration under typical conditions, its contribution is small compared to the major species **24**. Furthermore, [Pd(PPh$_3$)$_2$Cl]$^-$ was found to be more reactive than [Pd(PPh$_3$)$_2$Br]$^-$ towards oxidative addition with PhI. These results will be discussed further in Section 4.2.4.

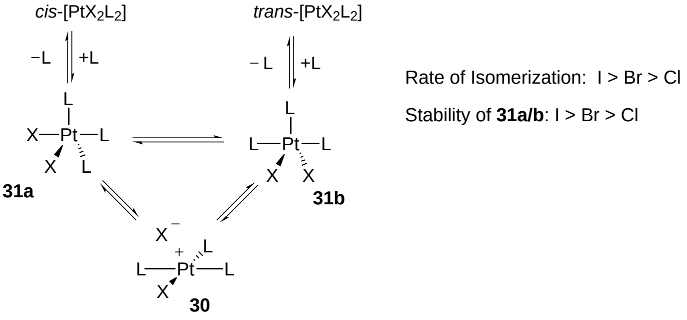
3.8. *cis–trans* Isomerization at Square-Planar d^8 Complexes

The mechanism of phosphane catalyzed *cis–trans* isomerizations of square-planar d^8 complexes has been the focus of detailed study [Eq. (1) X = halide, L = phosphane, M = Pd^{II}, Pt^{II}). Instead of one distinct mechanism emerging, conflicting results and interpretations have led to the proposal of at least four different possibilities[50] with each likely occurring to some extent depending on the exact conditions used during the study.[51] A feature of the associative mechanism is the transiency or intermediacy of a five-coordinate species [ML$_3$X$_2$]. The nature of the X ligand was found to influence the rate and probably the mechanism of these isomerizations.



(1)

Most mechanistic discussion has focused on the consecutive-displacement[50a–e] and pseudorotation[50f–i] pathways (Scheme 17) and it has been proposed that the dominant



Scheme 17. Mechanism of phosphane/halide-catalyzed *cis–trans* isomerization of [PtX$_2$L$_2$].

pathway depends on the coordinating ability of the X ligand, the basicity of the L ligand, and the polarity of the solvent.[50j] For example, it has been determined that the rate of isomerization is fastest when X = I. This result has been explained[50i, 52] as being a function of two factors. First, the five-coordinate complex is most stabilized when X = I, thus allowing sufficient time for pseudorotation to occur. Second, I^- is the most nucleophilic of the halides. Following the consecutive-displacement mechanism, this would mean that displacement of a more strongly bound neutral ligand on **30** will be fastest when X = I.

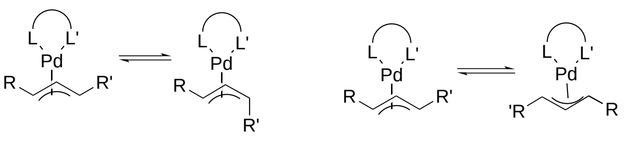
The intermediacy of complexes **30** and **31 a/b** warrants consideration since analogous five-coordinate complexes can be invoked as intermediates in other palladium-catalyzed transformations. Regardless of the exact mechanism, experimental evidence has revealed a significant halide effect in determining the complex that will most likely be formed. X-ray crystal structures have been determined for several compounds of empirical formula $[MX_2L_3]$ **31 a/b** when X = Cl and Br.[50i, 52, 53] In each case, the complexes exhibited a distorted square-pyramidal structure with the halide being located at the apex. Importantly, the metal–halide bond length at the apex was longer then the sum of the ionic radii calling into question whether these complexes are really five-coordinate or actually ionic and better described as $[MXL_3]^+X^-$. It has been pointed out, however, that while ion pairs are traditionally described as outer-sphere complexes, ion-pairs of four-coordinate complexes would probably not meet this description because of the coordinative unsaturation of d^8 complexes which allows the counter ion to enter the coordination sphere.

Roulet et al. have reported mechanistic studies of the phosphane-catalyzed *cis–trans* isomerization of square-planar $[PtX_2L_2]$ complexes (X = Cl, Br, I; L = PMe_3, PEt_3, $P(n\text{Bu}_3)$, $P(o\text{-tol})_3$).[52] When X = Cl or Br, the only species detectable in solution that contains three phosphanes was the square-planar **30**. However, when X = I, $[PtI_2(PMe_3)_3]$ could be detected as a five-coordinate complex in solution. Furthermore the addition of increasing amounts of NBu_4I to a solution of $[PtI(PMe_3)_3]PF_6$ gradually shifts the $^{31}P\{^1H\}$ NMR spectrum to that corresponding to the five-coordinate species $[PtI_2(PMe_3)_3]$. Although phosphane displacement is not observed at −60 °C, NMR spectroscopic analysis determined that fast exchange of I^- ions was occurring between the four- and five-coordinate complexes.

Studies have revealed that both steric[54] and electronic[55] factors play a role in determining whether a d^8 complex will be four- or five-coordinate. Larger ligands will favor the four-coordinate form so as to minimize steric interactions. From an electronic point of view, strong σ-donor and π-acidic ligands are expected to favor five-coordinate complexes. In the case of the halides, it appears that the electronic factors dominate since iodide results in the most stable five-coordinate complexes and iodide is the strongest σ donor. The halides are π donating, so they would all be expected to disfavor five-coordinate complexes, but since iodide is the weakest π donor this destabilization would be smallest when X = I. It is important to note that the size of the neutral ligands will also influence the relative stability of the four- and five-coordinate complexes. As these ligands become larger, the four-coordinate form will become increasingly preferred and the five-coordinate form increasingly short-lived.

3.9. Isomerizations of π-Allyl Palladium Complexes

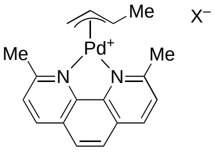
Significant advances towards an understanding of the mechanism of π-allyl palladium transformations have been made through the use of solution NMR spectroscopy and X-ray crystallographic analysis. The ability to isolate crystalline π-allyl intermediates was facilitated by the use of noncoordinating counter ions. As a result of the mechanistic work on π-allyl palladium species two key dynamic processes were revealed: *syn–anti* isomerization and apparent rotation (or *syn,syn–anti,anti* exchange; Scheme 18).[56]



syn-anti isomerization apparent rotation

Scheme 18. Important dynamic processes of π-allyl complexes.

In the studies of these two processes, a dramatic influence of the counter ion on the rate was observed.[57] For example, the *syn–anti* isomerization of complex **32** (BF_4^- counter ion) was found to be slow at room temperature facilitating isolation of the pure *syn* and *anti* isomers (Scheme 19).[58] At 60 °C slow isomerization was observed to afford an equilibrium mixture (2:1 ratio) of *syn:anti* **32** after several hours.



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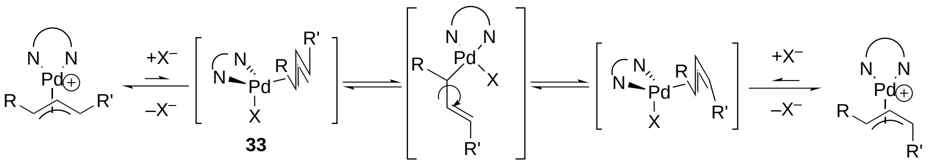
Counter Ion (X^-)	Properties
BF_4^-	Inert toward isomerization at 298K Slow isomerization at 333K
Cl^- (4 mol%)	Complete isomerization within minutes at 298K

Scheme 19. Effect of chloride on *syn–anti* isomerization.

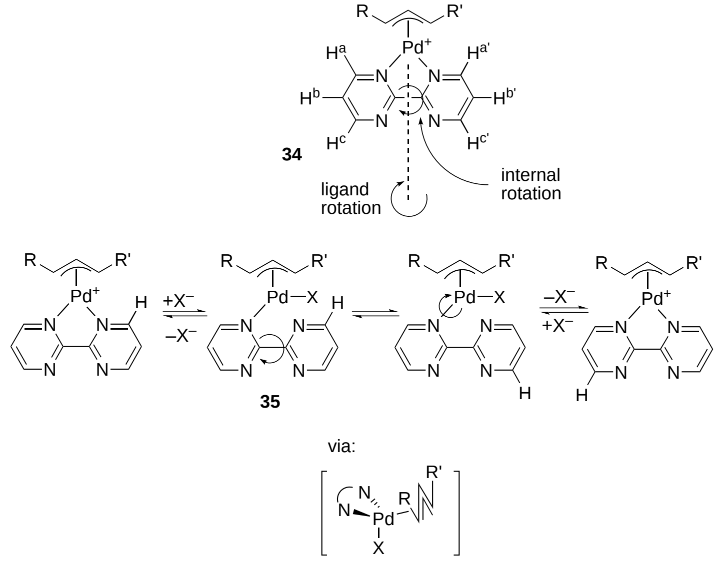
Importantly, when only 4 mol % Cl^- ion was added to the BF_4^- salt, complete equilibration was observed within minutes at room temperature. It was also determined that changing the solvent from tetrachloroethane to D_2O decreased the rate of isomerization by two orders of magnitude. This effect was attributed to the ability of water to stabilize the cationic four-coordinate π-allyl complex by efficiently solvating the ions and preventing the chloride from entering the palladium coordination sphere.[57c]

Insight into the mechanistic pathway was gained when it was determined that the entropy of activation for *syn–anti* proton exchange is negative; indicative of an associative process, opposite to that expected for the η^3-η^1-η^3 rearrangement[59] which results in an increase in entropy on conversion into the η^1-form. Furthermore, the rate of isomerization was found to increase proportionally to the amount of chloride added. These findings support the intermediacy of five-coordinate species **33** (Scheme 20). Intermediate **33** could then adopt the η^1-form reestablishing the four-coordinate square planar geometry and undergo subsequent *syn–anti* isomerization.

The mechanism established for the apparent rotation of π-allyl palladium species is analogous to that described above for the *syn–anti* isomerization.[60] Conclusive evidence for dissociation of one of the nitrogen atoms of the neutral ligand was obtained by solution NMR spectroscopy analysis for complex **34** (Scheme 21).[57d] At room temperature, only two aromatic protons were observed in a 2:1 ratio indicating that protons H^{a}, H$^{a'}$, H^{c}, and H$^{c'}$ were chemically equivalent. For H^{a} to be equivalent to H$^{a'}$ (and similarly H^{c} to H$^{c'}$) dissociation of one nitrogen atom must occur. The dissociated neutral four-coordinate species **35** is then free to undergo both internal and ligand rotation to make the protons equivalent in accord with the NMR spectroscopy observations. As with *syn–anti* isomerization, the rate of this exchange was found to be slow when the counter ion was noncoordinating and fast when chloride ions were added. The intermediacy of a five-coordinate species again explains these results. The same observations and explanations were made with respect to methyl exchange when tetramethylethylenediamine (TMEDA) is used as the ligand.



Scheme 20. Mechanism of *syn–anti* isomerization.



Scheme 21. Mechanism of apparent rotation.

4. Catalytic Processes: Improving Reactivity Through the Application of Halide Effects

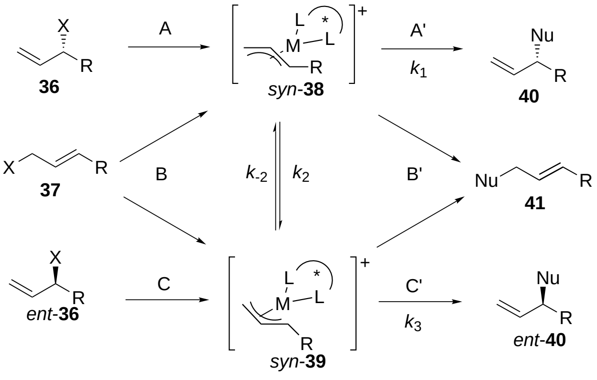
4.1. Halide Ligands and Asymmetric Catalysis

4.1.1. Palladium-Catalysis

4.1.1.1. Asymmetric Allylic Alkylations

Allylic bond formation through the intermediacy of π-allyl palladium complexes is an important synthetic transformation and remains an area of intense research.[61] Catalytic reactions, particularly enantioselective variants, based on the pioneering work of Tsuji and Trost[62] have received the most focus. While it is possible to pinpoint the source of enantioselectivity in several transition metal catalyzed processes, it is a much more complicated issue with allylic alkylations. In these processes, one or several of the steps in the mechanism may be the enantiodiscriminating step(s).[63] The choice of metal can also influence the nature of the enantioselective step through a change in reaction mechanism.[64, 65]

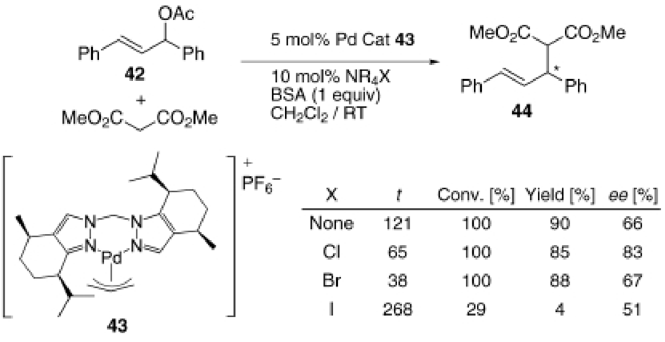
The issue is further complicated when substrates generate nonsymmetrical π-allyl intermediates since the complexes no longer possess a plane of symmetry when C_2-symmetric ligands are used. These substrates also give rise to regioselectivity issues since the two terminal carbons of the π-allyl group are not equivalent. These complexities are illustrated in Scheme 22. Upon reaction of the chiral π-allyl precursors, **36** and *ent*-**36**, displacement of the leaving group and inversion would generate predominantly *syn*-**38** and *syn*-**39** by pathways A and C respectively. The π-allyl precursor **37** is not chiral so displacement can occur from either olefinic face generating both *syn*-**38** and *syn*-**39**. At this point, nucleophilic attack with inversion could occur at the more substituted terminus of the π-allyl moieties to give **40** and *ent*-**40** (paths A′ and C′). If nucleophilic attack occurs at the less substituted terminus, achiral **41** would be generated from both intermediates (path B′).



Scheme 22. Factors affecting regio- and enantioselectivity of allylic substitution reactions. Nu = nucleophile.

Regioselectivity issues aside, two key prerequisites must be established for high enantioselectivity to be obtained in the formation of **40** commencing from rac-**36**. First, the chiral ligand must impart a sufficiently large difference in the rates of nucleophilic attack such that $k_1 \gg k_3$ or $k_3 \gg k_1$. Second, the rate of isomerization between the π-allyl intermediates, k_2 and k_{-2}, must be fast compared to nucleophilic attack, that is, Curtin–Hammett conditions must be established.[66, 67] The processes for the interconversion of *syn*-**38** and *syn*-**39** and the role that halides can play in them are discussed in Section 3.9.

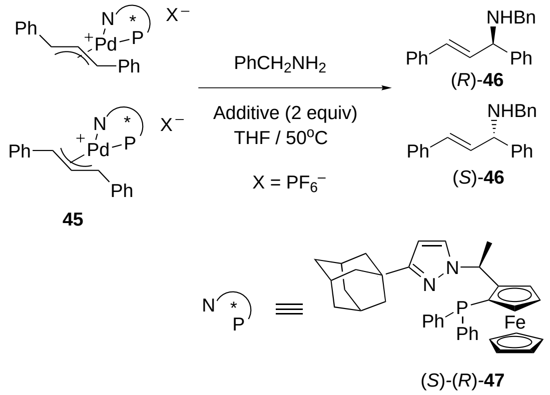
The first example of halide effects in asymmetric allylic alkylation reactions was reported in 1993.[68] In the reaction of **42** with dimethylmalonate in the presence of catalytic **43**, Togni and co-workers found that both the rate and the enantioselectivity were effected by the presence of added halides (Scheme 23). In the absence of added halide, complete conversion was observed after 121 hours and the desired product **44** was obtained in 90 % yield and 66 % *ee*. Better results were obtained when 5 mol % tetraethylammonium chloride was added. In this case, the reaction time shortened to 65 hours and the *ee* value increased to 83 %. Bromide induces slightly lower levels of enantioselectivity but a faster reaction, and iodide was found to be the worst, acting to poison the catalyst and lower the enantioselectivity to a lower level than when no halide additive was used.



X	*t*	Conv. [%]	Yield [%]	*ee* [%]
None	121	100	90	66
Cl	65	100	85	83
Br	38	100	88	67
I	268	29	4	51

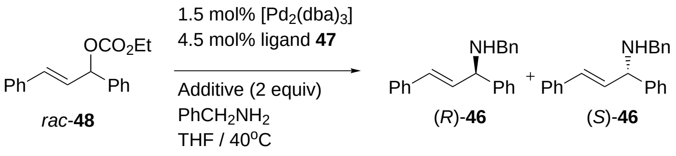
Another example of these halide effects was found by Togni and co-workers while working to understand the sense of induction in allylic alkylations of complex **45**.[69] When **45** is generated catalytically in situ, high enantioselectivities are observed for the generation of (*R*)-**46**. When the PF_6^- salt of **45**, isolated as a mixture of predominantly two isomers, is subjected to the reaction conditions, (*R*)-**46** is produced in < 10 % *ee*. To explain these results, two types of experiment were preformed to determine the influence of anions on the reaction outcome. In the first approach, the nucleophile was added to complex **45** (two isomers) along with various additives (Scheme 24). In the absence of any additive, **45** reacted to give (*R*)-**46** in 6.7 % *ee*. When two equivalents of fluoride were added, (*R*)-**46** was produced in 98.7 % *ee*. With borohydride as a counter ion, the *ee* value reached > 99.5 %.

The second approach focused on the effects of salt additives on the catalytic reaction (which already showed a high *ee* value). Again, the addition of small, hard anions caused an increase in the enantioselectivity (Scheme 25). It is intriguing that the addition of weakly coordinating counter ions caused a decrease in the enantioselectivity compared to when no additive was used.[70]



Additive	(*R*)-**46**:(*S*)-**46**	*ee* [%]
None	1.14:1	6.7
NBu_4OH	2.85:1	48
NBu_4F	153:1	98.7
NBu_4BH_4	>400:1	>99.5

Scheme 24. Effect of halides on enantioselectivity (stoichiometric amount of palladium).

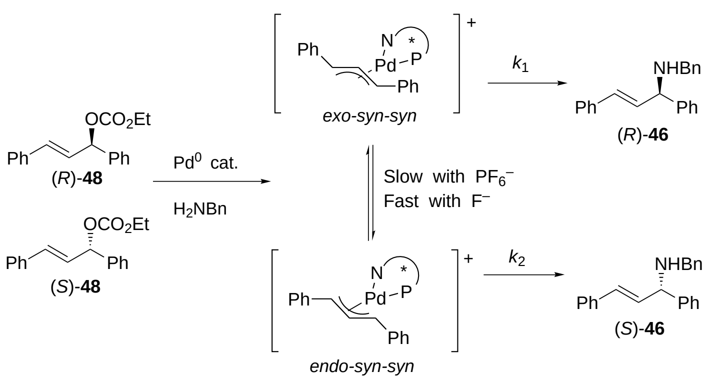


Additive	(*R*)-**46**:(*S*)-**46**	*ee* [%]	Additive	(*R*)-**46**:(*S*)-**46**	*ee* [%]
None	221:1	99.1	NBu_4Cl	221:1	99.1
NBu_4PF_6	5.25:1	68	NBu_4F	>400:1	99.5
NBu_4I	124:1	98.4	NBu_4OH	400:1	99.5
NBu_4Br	73:1	97.3	NBu_4BH_4	>400:1	>99.5

Scheme 25. Effect of halides on enantioselectivity (catalytic amount of palladium).

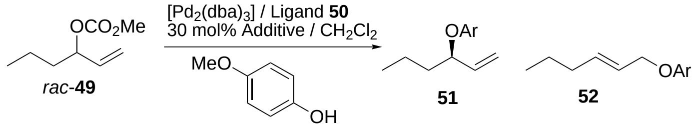
Togni argued that in the absence of coordinating counter ions, equilibration between the *endo-syn-syn* and the more stable *exo-syn-syn* π-allyl palladium intermediates is slow. Upon addition of such ions, however, interconversion becomes rapid compared to the rate of nucleophilic attack allowing Curtin–Hammett conditions to be established (Scheme 26).[71] These experiments clearly demonstrate the importance of fast equilibration of the π-allyl intermediates relative to nucleophilic attack for obtaining high enantioselectivity. Furthermore, they confirmed earlier predictions that the rates of apparent rotation and *syn*–*anti* isomerization are key factors to be considered in the development of new enantioselective π-allyl transformations.

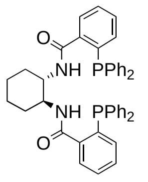
Recent application of this concept to the more challenging unsymmetrically substituted substrates has been reported by Trost and Toste.[72] Here too, the addition of a catalytic amount of halide was found to beneficially influence both the



Scheme 26. Proposed role of the halide effect in the asymmetric allylic substitution.

regioselectivity and the enantioselectivity (Scheme 27). For example, when *rac*-**49** is treated with *p*-methoxyphenol in the presence of catalytic amounts of Pd^0 and chiral ligand **50** in dichloromethane, the two regioisomeric products **51** and **52** are produced in a 67:33 ratio with **51** formed in only 36 % *ee*. Various salt additives were examined and it was found that chloride gave **51** and **52** in an 84:16 regioisomeric ratio with the major isomer produced in 83 % *ee*. These results parallel those of Togni with the enantioselectivity being highest for X = Cl. The effect of fluoride was not reported.





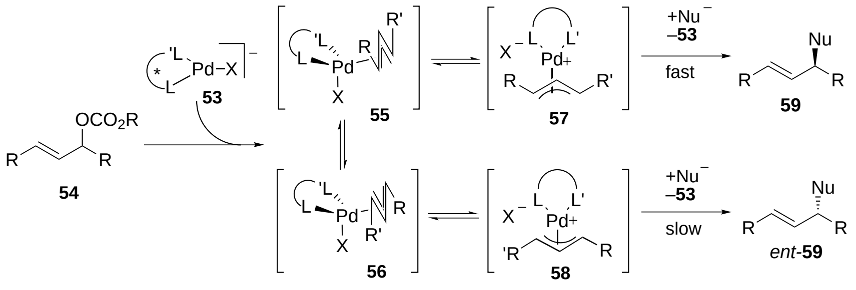
50

Additive	**51**:**52**	*ee* (**51**) [%]
None	67:33	36
$Bu_4N^+ClO_4^-$	71:29	59
$Bu_4N^+I^-$	84:16	75
$Bu_4N^+Br^-$	88:12	77
$Bu_4N^+Cl^-$	84:16	83

Scheme 27. Effect of halides on regio- and enantioselectivity.

Other factors that influence the selectivity of these transformations include the counter ion associated with the halide additives, the reaction concentration as well as the choice of solvent. All of these factors were found to influence the creation of Curtin–Hammett conditions.

Why it is that the lighter halides produce the highest enantioselectivities in π-allyl chemistry is a matter of conjecture. When the recent mechanistic work by Amatore and Jutand[49] on anionic palladium intermediates is taken into consideration along with the work done in studying the mechanism of *cis–trans* isomerization of d^8 square-planar complexes (Section 3.8), a slightly modified mechanistic pathway for the halide effect in π-allyl palladium chemistry may be put forward (Scheme 28). The active catalyst could be an anionic palladium–halide complex **53**, analogous to the active species proposed for the palladium-catalyzed coupling reactions. The additional electron density resulting from the binding of the halide to the Pd^0 species should also make oxidative addition a more favorable process. The first species generated upon oxidative addition would thus be the neutral π-allyl complexes **55** and **56**. Loss of halide from **55** and **56** would produce **57** and **58** which would probably exist as ion pairs with the halide counter ion. Analogous to the *cis–trans* isomerization proposals, the coordinative unsaturation of the d^8 square-planar palladium complex may allow the halide to enter the coordination sphere facilitating the formation of the five-coordinate intermediates. Nucleophilic attack would most likely occur at the cationic complexes **57** and **58** since they are more electrophilic. The anionic **53** would thus be regenerated and react with another **54**. Given that the environment around the metal center in **57** and **58** is likely to be sterically congested, the faster isomerizations by F and Cl may be in part because of their smaller size and better ability to form tight ion pairs. The ability of the halide to enter the coordination sphere would also influence the electrophilicity of complexes **57** and **58** by reducing the positive charge at the metal center. A less reactive π-allyl complex would enhance the ability of the system to attain Curtin–Hammett conditions.

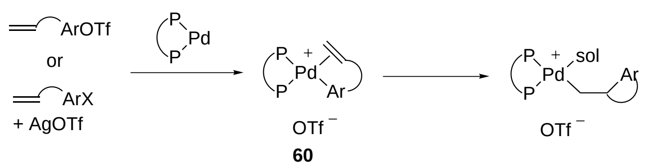


Scheme 28. Alternate mechanism for the halide effect in Pd-Catalyzed asymmetric allylic substitution.

4.1.1.2. Asymmetric Heck Reactions

The Heck reaction has become an increasingly useful method of carbon–carbon bond formation and remains an exciting area of study in organic synthesis.[73, 74] Because these reactions were rarely used to generate stereocenters[75] and the belief that chelating bisphosphane ligands were unsuitable,[76] the first asymmetric Heck reactions were only described in 1989.[77] Since then, significant advances have been made and enantioselectivities in excess of 90 % have been reported in certain cases.[78]

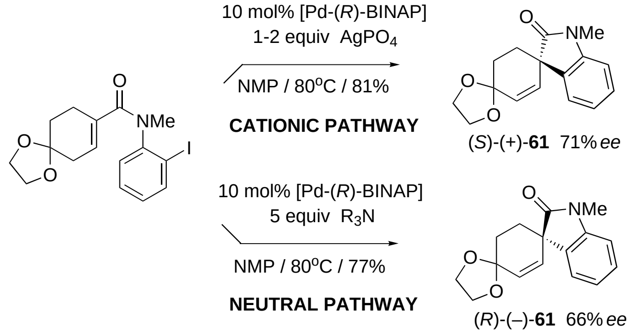
Some of the best results have been obtained using conditions where the reaction is believed to proceed by a cationic pathway (Scheme 29).[79] The use of aryl or vinyl triflates, or aryl or vinyl halides in combination with a halide scavenger (such as silver or thallium salts) frees a coordination site and facilitates binding of the chiral bidentate ligand,



Scheme 29. Cationic pathway for the asymmetric Heck reaction. OTf = OSO_2CF_3 = triflate, sol = solvent.

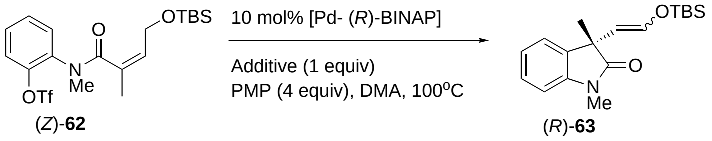
the olefin, and the aryl group to give the key Pd^{II} intermediate **60**.[80]

In 1992, Overman and co-workers reported an asymmetric Heck reaction that generated spirocycle **61**. In this case, it was found that either enantiomer could be formed with good selectivity using the same enantiomer of 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (BINAP) depending on the base use to scavenge HI (Scheme 30).[81] When silver salts were used, the reaction proceeded by the cationic pathway to produce (*S*)-(+)-**61** in 71 % *ee*. When tertiary amines were used as the HI scavenger, (*R*)-(−)-**61** was generated in 66 % *ee*. The iodide remains in the reaction mixture as an amine hydroiodide and could still interact with the palladium catalyst. Under these conditions, the reaction was suggested to proceed by a neutral pathway.



Scheme 30. Dependence of enantioselectivity on presence of halide ions. NMP = *N*-methylpyrrolidone.

Studies on a similar system also demonstrate the beneficial effects of added halides (Scheme 31). When aryl triflate **62** is subjected to palladium catalysis in the absence of any salt additives, the oxindole **63** is formed in 72 % yield and 43 % *ee*.

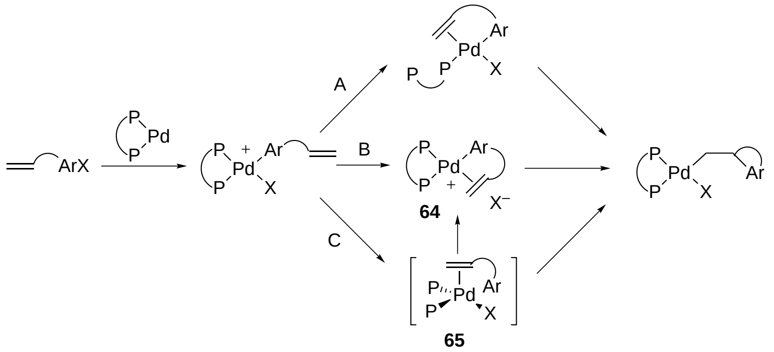


Additive	Yield [%]	*ee* [%]
None	72	43
Bu_4NOTf	70	42
Bu_4NCl	52	93
Bu_4NBr	59	93
Bu_4NI	62	90

Scheme 31. Effect of added halides in the asymmetric Heck reaction. PMP = 1,2,2,6,6-pentamethylpipridine, DMA = dimethylacetamide, TBS = *tert*-butyldimethylsilyl.

Addition of Bu_4NOTf (OTf = OSO_2CF_3 = triflate) shows no improvement, but use of ammonium halides causes the enantioselectivity to increase to > 90 % *ee*.

Within the neutral pathway, there are at least three possible routes that could lead to product formation (Scheme 32). While path A had been the presumed mode of action for the neutral Heck reaction, this was ruled out as phosphane dissociation or partial dissociation would presumably result in an erosion of enantioselectivity (verified experimentally by using mono-phosphane analogues of BINAP which gave lower levels of induction).[81d] Path B would lead to ionic intermediate **64** where the halide has dissociated from the metal center. This too was ruled out as similar selectivity should be expected from iodide salt **64** (X = I) and triflate salt **60** if the counter ions were fully dissociated (supported experimentally). The authors favor Path C which passes through the pentacoordinate Pd^{II} species **65**. Since substitution chemistry at square-planar Pd^{II} species occurs predominantly through associative processes,[82] axial coordination of the olefin could occur giving rise to **65**. Migratory insertion at five-coordinate **65** is energetically less favorable,[83] thus direct product formation from **65** was ruled out. Another possibility is that displacement of the halide by the olefin could occur to give **64** that could then form the product. It is this process of halide displacement by the olefin that the authors favor as the enantiodiscriminating step thus differentiating it from the cationic pathway.



Scheme 32. Proposed reaction pathway under neutral conditions.

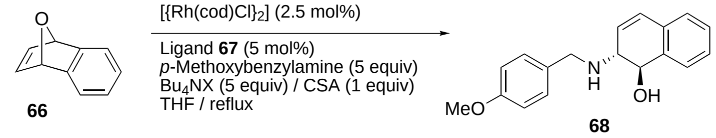
While direct product formation from **65** was regarded as being less likely than the conversion of **65** into **64**, recent results with asymmetric ene-type cyclizations of a 1,6-enyne may indicate that this path should not be ruled out. Mikami and co-workers have found that by varying the reaction conditions, high enantioselectivities (> 90 % *ee*) can be obtained from both the four-coordinate cationic intermediate (analogous to **64**) and the five-coordinate neutral complex (analogous to **65**) when X is trifluoroacetate.[84]

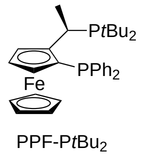
4.1.2. Rhodium and Iridium Catalysis

4.1.2.1. Asymmetric Ring-Opening Reactions

As part of a research program aimed at the development of new asymmetric heteroatom additions to strained olefins,[85] we found a dramatic halide effect in the rhodium-catalyzed asymmetric ring opening (ARO) of oxabenzonorbornadiene **66**. While alcohols and phenols could be used as nucleophiles to induce ring opening in good yield and high *ee* values amines, were problematic. For example, activated amines gave good yield, but poor *ee* values with a catalyst generated in situ from [{Rh(cod)Cl}$_2$] (cod = cycloocta-1,5-diene) and PPF-P*t*Bu$_2$ (**67**; PPF = 1-[2-(diphenylphosphanyl)ferrocenyl]-ethane). With the same catalyst, aliphatic amines did not react at all because of catalyst poisoning. This trend in reactivity was also observed in our rhodium-catalyzed ring-opening reactions of vinyl epoxides.[86] In an effort to overcome catalyst poisoning, the use of additives was examined. It was found that the combined use of protic and halide additives effectively alleviate the poisoning. The choice of halide was found to be important, fluoride did not result in the formation of product with aliphatic amine nucleophiles. Other halides led to an increase in reactivity according to the trend Cl < Br < I. The halide additive was found to have a pronounced effect on the enantioselectivity of these transformations (Scheme 33). With *p*-methoxybenzylamine, for example, ligand **67** gives **68** in 29% *ee* with chloride as the halide additive, and 42% with bromide. Addition of iodide gives the best result, producing **68** in 72% *ee*. This value can be improved to 81% if the chloride is first removed by the addition of a silver salt prior to the addition of iodide.

The choice of halide may be used to increase the enantioselectivity with more acidic amine nucleophiles. While the addition of halide or proton additives is not required when activated amines are used, changing the halide ligand on the metal center prior to the addition of reagents leads to a dramatic increase in the enantioselectivity. With phthalimide, for example, the *ee* value increases by 54% to give **69** in 98% *ee* (Scheme 34). This tendency was found to be general for a variety of activated amines.[87]

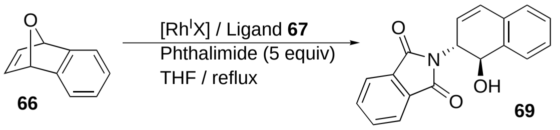




PPF-P*t*Bu$_2$
67

X	Yield [%]	*ee* [%]
F	no reaction	–
Cl	52	29
Br	67	42
I	72	72

Scheme 33. Effect of halides on aliphatic amine asymmetric-ring opening. CSA = D-10-caphorsulfonic acid.

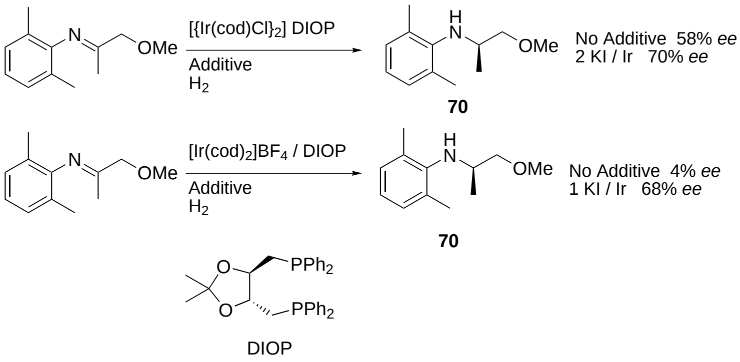


X	Yield [%]	*ee* [%]
Cl	55	45
Br	78	79
I	90	98

Scheme 34. Effect of halide ligands on activated amine asymmetric ring opening.

4.1.2.2. Asymmetric Hydrogenations

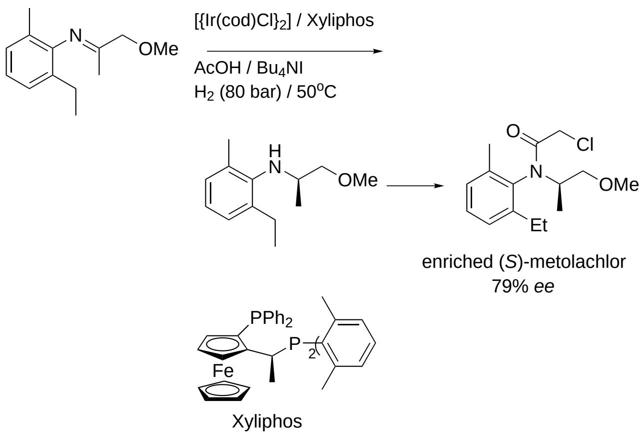
With the goal of establishing a chiral synthesis for the pesticide metolachlor, an iridium-catalyzed reduction of imines was developed which showed a pronounced halide effect.[88] In an initial report, improved yields and enantioselectivities were obtained with the addition of 1–2 equivalents of iodide relative to iridium. For example, when [{Ir(cod)Cl}$_2$] and bis[(diphenylphosphanyl)methyl]-2,2-dimethyl-1,3-dioxolane-4,5-diol (DIOP) are used in the absence of an additive, **70** is obtained in 58% *ee*. When iodide was added, the enantioselectivity improved to 70% (Scheme 35). An even more pronounced halide effect was observed when the cationic [Ir(cod)$_2$]BF$_4$/DIOP catalyst was used. In this case in the absence of an additive **70** was obtained in only 4% *ee*. When iodide was added the enantioselectivity increased to 68%. It was noted that the addition of iodide afforded better results than chloride or bromide.



Scheme 35. Halide effects in imine hydrogenations.

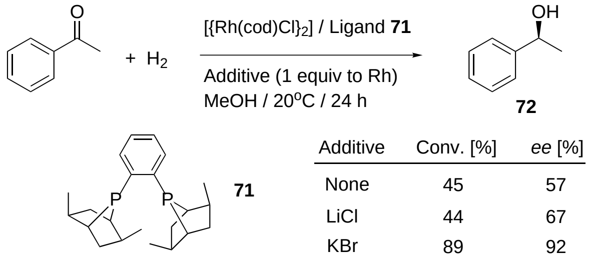
The optimized process for the commercial production of enantiomerically enriched metolachlor operates at a hydrogen pressure of 80 bar at 50 °C with an in situ generated catalyst from [{Ir(cod)Cl}$_2$] and the ferrocenyldiphosphane ligand xyliphos (Scheme 36). For optimal results, Bu$_4$NI and acetic acid are used which reduce the reaction time 20-fold. Exceptionally low catalyst loading can be used. Typical substrate/catalyst ratios are as high as 1000000:1 and the turnover frequency (TOF) is an outstanding 350000 h^{-1}.[89]

Analogous halide effects have been reported with a rhodium-catalyzed hydrogenation of imines[90] and, more recently, with ketones.[91] Using an in situ generated catalyst from [Rh(nbd)Cl]$_2$ (nbd = norboradiene), the chiral ligand 1-cyclohexyl-1,2-bis(diphenylphosphanyl)ethane (cycphos)[92] and an equivalent of halide, noticeable differences in enantioselectivity were observed. When no additional halide was added, with chloride still as the counter ion, the hydrogenated product was obtained in 67% *ee*. This value increased to 72% *ee* when bromide was added and 79% when iodide was used. The halide effect using a [{Rh(cod)Cl}$_2$]/ligand **71** catalyst for the hydrogenation of ketones is more



Scheme 36. Halide effects in the industrial preparation of metolachlor.

pronounced (Scheme 37). In the absence of an additive, acetophenone is hydrogenated to generate alcohol **72** with 45% conversion and 57% *ee* after 24 hours. With one equivalent LiCl (relative to rhodium), **72** is produced with slightly better *ee* value of 67%, in similar conversion under identical conditions. Optimal results were obtained with KBr, with the product formed in 92% *ee* and 85% conversion. No mention was made of the use of iodide. In addition to halides, amine bases were also found to have beneficial effects on both the reactivity and enantioselectivity.



Additive	Conv. [%]	*ee* [%]
None	45	57
LiCl	44	67
KBr	89	92

Scheme 37. Effect of halide additives on rhodium-catalyzed ketone hydrogenation.

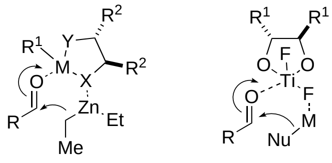
4.1.3. Transition Metal Fluoride Catalysts

4.1.3.1. Special Properties of the Fluoride Ligand and Fluorine–Metal Complexes

Transition metal fluoro compounds exhibit interesting properties as a result of the fluoride ligand. Experimental evidence indicates that the fluoride ligand confers substantially different properties to the complex compared to the other halide ions. This difference in reactivity has prompted reviews of the chemistry of these complexes[93] and their application in asymmetric catalysis.[94] Since these reviews are comprehensive, the chemistry of fluoride complexes will be briefly described here and only reactions where the metal–fluoride complex is the active catalyst will be included.

4.1.3.2. Asymmetric Additions to Aldehydes

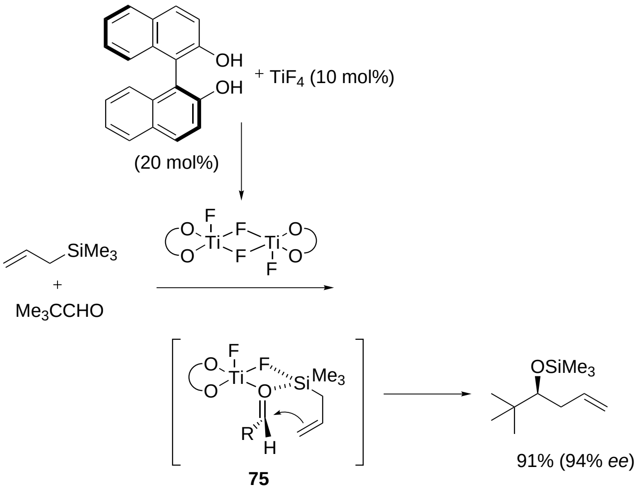
A common feature of successful catalysts for the enantioselective addition of dialkylzinc reagents to aldehydes is that one of the heteroatom donors in chelate **73** acts as a bridging ligand between the electrophilic metal center and the dialkylzinc species. This complexation not only increases the electrophilicity of the aldehyde and the nucleophilicity of the alkylzinc unit, but also allows the formation of an ordered transition state (Scheme 38).[95] Given the propensity for fluoride to act as a bridging ligand, if complexes such as **74** could be formed, high selectivities could be anticipated.[96]



73 **74**

Scheme 38. Bridging structures in the asymmetric addition to aldehydes.

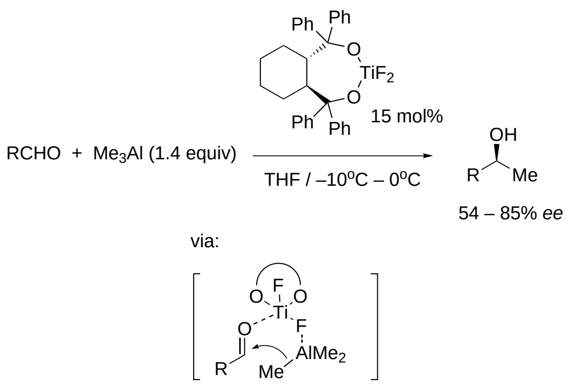
Carreira and Gauthier described a titanium–fluoride catalyst for the addition of allyltrimethylsilane to aldehydes. Using a catalyst derived from TiF$_4$ and 2,2′-dihydroxy-1,1′-binaphthyl (BINOL), enantioselectivities up to 94% have been obtained (Scheme 39).[97] The importance of fluoride as a ligand in this reaction is demonstrated by the fact that complexes prepared with TiCl$_4$ and TiBr$_4$ are not active. This pronounced difference in reactivity was proposed to stem from the strong electron-withdrawing nature of the fluoride ligands and the strong Ti–F bond. This effect would result in the Ti center becoming more Lewis acidic and hence further activate the aldehyde to attack. Furthermore, the bridging ability of fluoride was proposed by Duthaler[84] to activate the silane as a nucleophile[98] and increase the facial selectivity through the formation of adduct **75**.



75

Scheme 39. Asymmetric allylsilation of aldehydes.

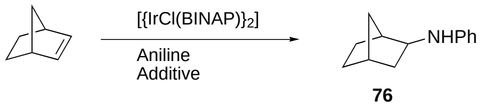
Another example illustrating this concept, described by Carreira and Pagenkopf, involves the enantioselective addition of trimethylaluminum to aldehydes in up to 85% *ee* (Scheme 40).[99] Given the affinity of aluminum for fluoride,[100] the formation of a fluoride bridge is again invoked to explain the reactivity.



Scheme 40. Asymmetric addition of trimethylaluminum to aldehydes.

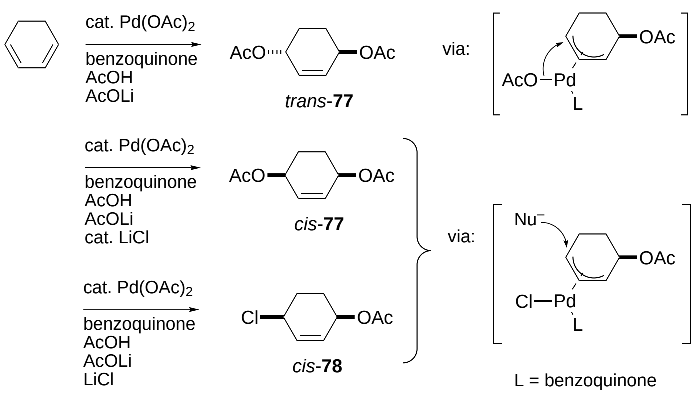
4.1.3.3. Asymmetric Hydroaminations

Togni and co-workers have also uncovered a dramatic halide effect in an asymmetric iridium-catalyzed hydroamination reaction where the use of fluoride was found to produce the optimal results.[101] The addition of four equivalents of fluoride gave **76** in 95% *ee* (Scheme 41). In the absence of fluoride the enantioselectivity was only 57% *ee*. It was mentioned that the use of chloride, bromide, or iodide in place of fluoride has either no effect or only detrimental effects on activity and enantioselectivity. It was proposed that the good π-donating ability of fluoride in addition to its tendency to form hydrogen bridges could enhance the ability of iridium(I) to undergo N–H insertion.



Additive	Yield [%]	*ee* [%]
None	12	57
$2\,F^-$ / Ir	45	78
$4\,F^-$ / Ir	22	95

Scheme 41. Halide effects in iridium-Catalyzed asymmetric hydroamination.



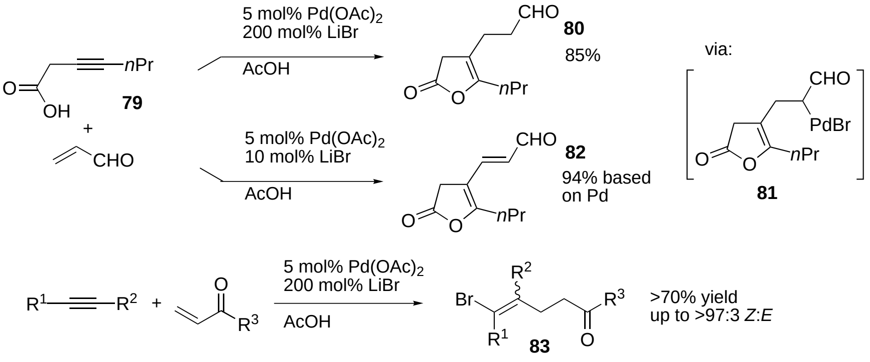
Scheme 42. Effect of halides on the acetoxypalladation reaction.

4.2. Halide Effects in Achiral Catalytic Processes

4.2.1. Diverting Reaction Pathways Through Coordination-Site Occupation

Bäckvall et al. have reported that 1,3-dienes can be regio- and stereoselectively functionalized at the 1,4-positions by palladium-catalyzed transformations (Scheme 42).[102] The first step in these reactions involves the *trans*-acetoxypalladation of one of the olefins to generate a π-allyl intermediate with the second olefin. Subsequent reaction of this intermediate was found to be highly sensitive to the relative amounts of lithium acetate and lithium chloride in the reaction mixture. When LiOAc is used as the nucleophile in the absence of LiCl, *trans*-**77** is produced by an intramolecular delivery of the acetate nucleophile from the palladium. When catalytic amounts of LiCl are added, the stereochemistry of the second acetate delivery is reversed. The authors propose that chloride ions bind preferentially to the palladium thus occupying the coordination site previously available to the acetate. Since intramolecular delivery of the acetate is blocked, intermolecular nucleophilic attack occurs with inversion to generate *cis*-**77**. When an excess of LiCl is used, *cis*-**78** becomes the product as a result of intermolecular nucleophilic attack by the chloride ion. In each of these cases, high selectivity for the 1,4-addition product is observed.[103] This inversion of stereochemistry because of the presence of halide ions was also observed in palladium-catalyzed 1,4-oxylactonizations.[104]

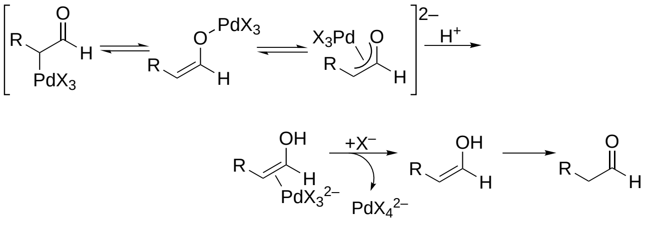
Lu and co-workers have reported that the use of excess halides can alter the reaction outcome of Heck-type couplings with *α*,*β* unsaturated carbonyl compounds. The typical pathway for Heck reactions involves a carbopalladation step followed by *β*-hydride elimination. When excess halide is present, the *β*-hydride elimination step is suppressed allowing protonolysis of the palladium enolate to occur in acidic media.[105] For example, when **79** is treated with acrolein in the presence of catalytic amounts of [Pd(OAc)$_2$] and 200 mol% LiBr, **80** is generated exclusively (Scheme 43). This product arises from the oxypalladation of the alkyne followed by carbopalladation of the acrolein to generate intermediate **81**. In the presence of 200 mol% LiBr, *β*-hydride elimination was effectively inhibited allowing protonolysis to occur. When



Scheme 43. Effect of excess halide on *β*-hydride suppression.

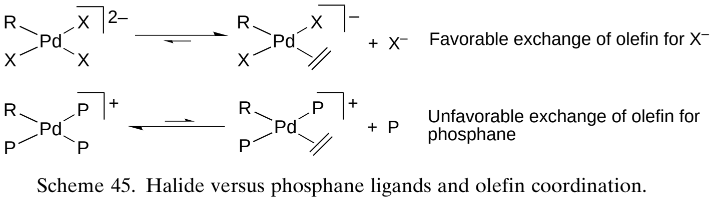
only 10 mol% LiBr is used, the typical Heck-type product **82** is formed by the standard β-hydride elimination pathway in 94% yield based on Pd.[106] An analogous reaction with alkynes and acrylates also allows selective protonolysis of the palladium-enolate intermediate to give **83**. This process has also been used to produce (E,Z)-γ,δ unsaturated carbonyl compounds.[107]

The effect of the nature of the anion was studied and it was found that LiOAc, LiF, and $LiClO_4$ all afforded the normal Heck-type product resulting from β-hydride elimination. LiCl, LiBr, and LiI, on the other hand, only gave the 1,4-addition products arising from protonation. Lu proposed that the protonation process is facilitated by three factors.[105] First, the presence of an excess of halide diminishes the β-elimination by occupation of the free coordination site. Second, the electron donation from the halide to the Pd center results in a highly polarized Pd–C bond which increases its susceptibility to protonation. Third, the palladium enolate is in equilibrium with a π-oxoallylpalladium form (Scheme 44) and the ionic nature of the Pd–O bond will facilitate protonation.



Scheme 44. Mechanism of halide suppression of β-hydride elimination.

Lu also drew attention to another important aspect of the use of halide ligands to prevent β-elimination. He noted that the same result cannot be achieved with the use of excess phosphane ligands since the addition of phosphanes shuts down the reaction by blocking the coordination of the olefin. The advantage of using halide ligands may result from the facile ligand exchange from a halide to an olefin while exchange of a phosphane for an olefin is very slow (Scheme 45).

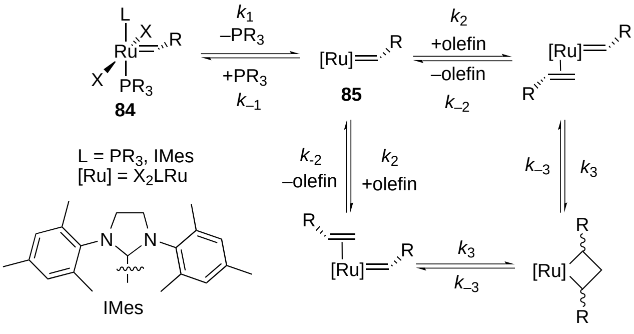


Scheme 45. Halide versus phosphane ligands and olefin coordination.

4.2.2. Olefin Metathesis

The past several years have seen a revolution in the field of olefin metathesis, largely a result of the discovery and application of air-stable catalysts.[108] The ruthenium catalysts developed by Grubbs and co-workers have found particularly widespread application, and the "first generation" bisphosphane complex **84** (L = PCy_3, R = Cy, X = Cl),[109] has recently been followed by a more reactive, second-generation complex **84** (L = N,N'-bis(2,4,6-trimethylphenyl)imidazolidine-2-yl (IMes), R = Cy, X = Cl).[110] Intense effort has been devoted to the mechanistic study of these reactions, with the hope of enabling the development of even more highly reactive catalysts. Recent work has shed light on the effect of the various ligands and has revealed the presence of a large halide effect for both generations of the Ru catalysts.

To probe the effect of ligands on the ruthenium metathesis catalysts $[L(PR_3)(X)_2Ru{=}CHR]$, a variety of different complexes **84** were prepared and each of the variables, L, R, and X, was found to influence the catalytic activity.[111] The halide ligands, in particular, were found to exert a dramatic effect on the phosphane dissociation required for catalyst initiation and generation of the propagating catalyst species **85** (Scheme 46). Changing the X ligands from chloride to iodide resulted in a 250-fold increase in phosphane dissociation (k_1). Changing from chloride to bromide also increased initiation, albeit by only a threefold difference. Grubbs attributed these differences in initiation to the relative size of the halides.[111] Since dissociation of PR_3 will be favored by an increase in steric congestion at the metal, the larger halides will favor this process.



Scheme 46. Halide effects in olefin metathesis.

While the diiodo complexes show the fastest initiation, their olefin metathesis activities are comparable or lower than that of the dichloride analogues despite the fact that the propagating species **85** is present in higher concentration. This result indicates that the propagating species **85** is significantly less active when X = I than when X = Cl. The difference in reactivity has been attributed to the ratio of k_{-1} to k_2. In both the first and second generation ruthenium catalysts, the change from the diiodide species to the dichloride resulted in a 100-fold increase in k_{-1}/k_2. While the reasons for this shift are not clearly understood, it has been suggested that olefin coordination may require a *trans* to *cis* isomerization of the X ligands.[112] This isomerization could be less favorable with large X ligands and result in a decrease in k_2 for the diiodo catalysts.

4.2.3. Olefin Isomerization

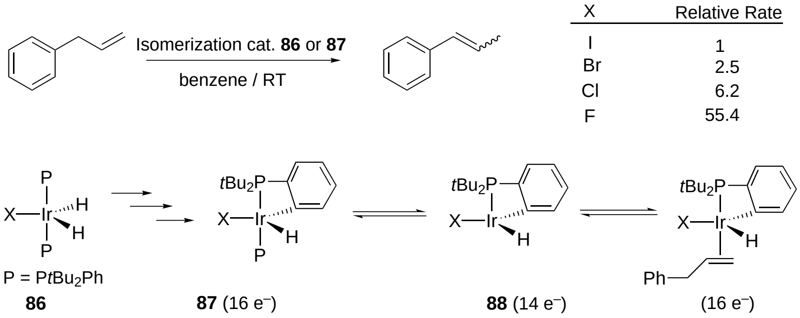
Caulton and Cooper have uncovered a significant halide effect in studies aimed at identifying the active olefin-isomerization catalyst when **86** is used as the catalyst precursor.[113] It was found that **87** could be isolated from the reaction and that

87 was also an active isomerization catalyst. It was determined that catalysts with better π-donating ligands were the most reactive and that the catalyst with X = F was most reactive (Scheme 47). The authors propose that this trend indicates that the rate-determining step involves a transition to a more highly unsaturated species **88**. Since the equilibrium constant for such a process would be highly influenced by the presence of a π-donating ligand, such a ligand would make the process more favorable and thus increase the concentration of the active 14-electron complex. On the contrary, if the rate-determining step would have involved the generation of a six-coordinate 18-electron d^6 species by coordination of the olefin directly to **87**, the opposite trend in dependence on the halide ligand would have been expected.

4.2.4. Palladium-Catalyzed Coupling Reactions

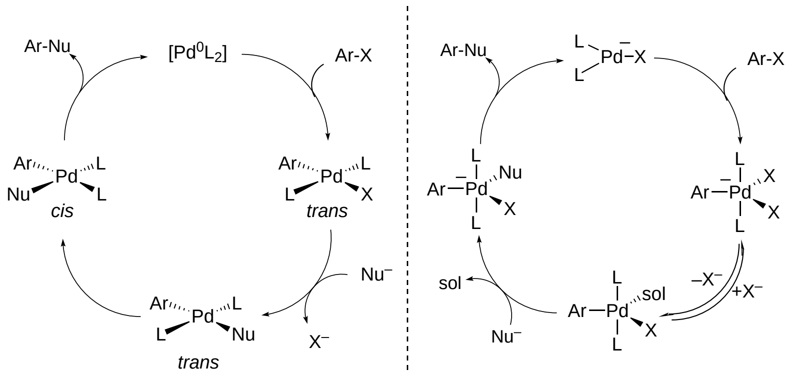
Palladium(0) catalysts are commonly used in a wide range of transformations including allylic substitution, aryl amination, Heck reactions, and Suzuki couplings. A typical catalyst precursor is $[Pd(PPh_3)_4]$ where the active catalyst is the coordinatively unsaturated 14-electron $[Pd(PPh_3)_2]$. Through the study of stoichiometric reactions, the reaction mechanism for palladium-catalyzed coupling reactions was established to include oxidative insertion, transmetallation, isomerization, and reductive elimination steps (Scheme 48, mechanism 1 in the absence of free halide). Even though evidence for each of the individual steps was obtained, proof that they were operative within the catalytic cycle was not demonstrated. Indeed, evidence revealed that this assumption was incorrect, at least in certain cases. For example, kinetic work indicated that the catalytic process for the entire cycle was faster than the substitution and reductive elimination processes that were supposed to lie within the catalytic cycle.[114] Evidence that another mechanism may be operating was obtained by Amatore, Azzabi, and Jutand[49] when it was determined that the rate of reaction of palladium(0) species generated by electrochemical reduction of $[PdX_2(PPh_3)_2]$ with PhI depended on the nature of the halide in the Pd^{II} precursor (see Section 3.7).

Further mechanistic work by Amatore and Jutand has produced a more accurate description of the catalytic cycle involved in palladium-catalyzed coupling reactions.[49] While the earlier proposed mechanism 1 may still operate under conditions free of halides (or acetate ions) or when an excess of phosphane is present (as when the catalyst precursor is $[Pd(PPh_3)_4]$), a new mechanism incorporating the newly obtained mechanistic information was put forward. Furthermore, even when mechanism 1 (Scheme 48) may operate early on in the reaction, if there is an accumulation of halide in the reaction mixture because of the consumption of the aryl halide, mechanism 2 will become operative and gradually become the predominant pathway for the reaction (Scheme 48). Important conclusions include that when such anionic ligands are present, $[Pd(PPh_3)_2]$ will not be present in solution but will be replaced by the $[Pd(PPh_3)_2X]^-$ ion. In addition, the halide ligand will be intimately involved in all of the key processes of the catalytic cycle and should therefore not be ignored.



X	Relative Rate
I	1
Br	2.5
Cl	6.2
F	55.4

Scheme 47. Effect of the halide ligand on the rate of olefin isomerization.



Scheme 48. Proposed mechanisms for palladium-Catalyzed cross-coupling reactions. Left: mechanism 1, cross-coupling without free halide or in the presence of excess phosphane. Right: mechanism 2 cross-coupling in presence of free halide.

5. Outlook

It is readily apparent that much more mechanistic work is required to fully understand the processes involved in halide effects, especially in the field of asymmetric catalysis. A better understanding of the processes would greatly assist chemists in the application of halide effects towards the development of new transformations.

Halides are much more than innocent ancillary ligands. Rather, the presence of the metal–halide group should be viewed as a highly valuable functionality that can allow fine-tuning of the catalyst's properties. The subtle changes imparted by varying the halide are often predictable and can be synthetically useful. The experimental evidence behind the notion of the metal–halide moiety as a *tunable functionality* on the catalyst species should be of considerable value for those working within the field of transition metal catalysis.

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